REMARKS

Applicants are in receipt of the Office Action mailed January 4, 2006, and have the following comments.

Rejection pursuant to 35 USC §102(b)

The Examiner has not met the burden of establishing a lack of novelty, since the prior art does not disclose prednisolone acetate as part of an ophthalmic composition in combination with a cyclodextrin or cyclodextrin derivative.

The Examiner has again rejected claims 31-36, 39-46 and 49-50 as allegedly anticipated over Loftsson et al., U.S. Patent. No. 5472,954. Applicants respectfully disagree for the following reasons.

A claim is not anticipated unless a single prior art reference contains each and every limitation of the claim and teaches a person of skill in the art to make and use the invention without undue experimentation. *See In re Paulsen*, 30 F.3d 1475, 31 USPQ 2d 1671 (Fed. Cir 1994). Thus, anticipation under 35 U.S.C. §102 requires identity of the claimed invention and the reference disclosure; there may be no differences between these, as viewed by the person or ordinary skill in the art in the field of the invention. See e.g., *Scripps Clinic & Res. Found. v. Genentech, Inc.*, 927 F.2d 1595, 18 USPQ2d 1001 (Fed. Cir. 1991).

Claim 31 is directed to an ophthalmic composition comprising a single, specific compound, prednisolone acetate, in combination and aqueous solution with a cyclodextrin. Claim 32 specifies that the cyclodextrin derivative is present in an amount sufficient to increase the solubility, to enhance the stability, or to reduce unwanted side

effects of the prednisolone acetate. Claim 33 specifies that the ophthalmic composition has an ophthalmically acceptable tonicity level, and claim 34 specifies that the composition has an ophthalmically acceptable pH. Claim 39 is drawn to the composition of claim 31 in which the composition comprises one of a Markush group of cyclodextrins and cyclodextrin derivatives. Claim 40 is drawn to the ophthalmic composition of claim 31 wherein the cyclodextrin derivative is sulfobutylether-β-cyclodextrin. Claims 41-50 are claims comprising methods of topically administering the compositions of claims 31-40.

Loftsson is drawn to a method for enhancing the complexation of a cyclodextrin with a lipophilic, water-labile, insoluble or sparingly soluble active ingredient; the active ingredient may be a drug. *Loftsson*, abstract and column 4, lines 3-8 and 16-19. With specific regard to the drug-containing formulations, Loftsson states that ophthalmic routes may be used. *Id.* at column 18, line 11 and column 19, lines 16-31. The Loftsson reference also lists a large set of compounds that it says may be used in the compositions it describes; one such compound is prednisolone. *Id.* at paragraph bridging columns 9 and 10. Loftsson also describes various cyclodextrin derivatives, including sulfobutylether-β-cyclodextrin. *Id.* at column 6, lines 50 to column 7, line 6.

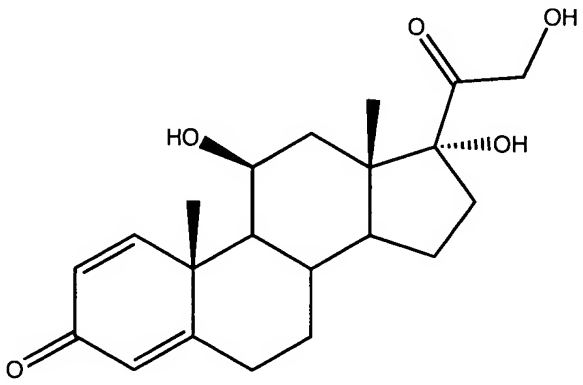
Prednisolone acetate is not a compound disclosed, either expressly or inherently by Loftsson; therefore Loftsson cannot anticipate claim 31, or any of the other pending claims.

Nevertheless, the Examiner has maintained the rejection, asserting a number of reasons. First, in the January 4, 2006 Office Action, the Merck Index 11th ed. pages 1223-1224 (1989) was cited for the proposition that "the compound prednisolone appears to be synonymous with

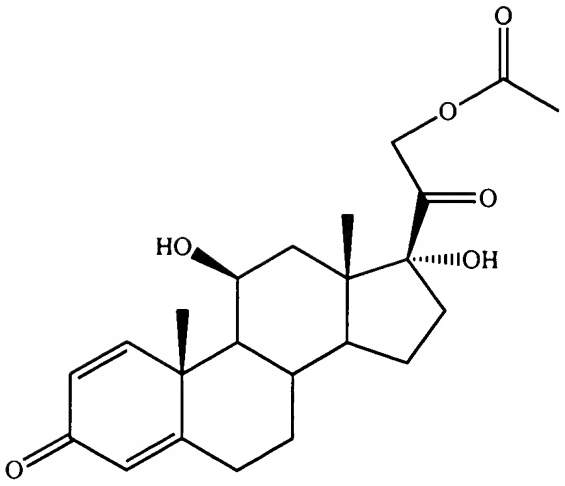
prednisolone acetate (see compound 7719, page 1223)." Office Action of January 4, 2006.

Page 1223 of the 11th edition of the Merck Index mentions prednisolone-21-acetate as a short entry under monograph number 7719 for prednisolone; however it also clearly describes the different physical characteristics of the two compounds, such as the decomposition temperature for the crystalline forms (240°-241° for prednisolone and 237°-239° for prednisolone acetate) and different optical rotations: (+102° for prednisolone and +116° for prednisolone acetate).

In the 37 CFR 1.116 Reply and Amendment of March 1, 2006, Applicants pointed out that prednisolone and prednisolone acetate have different chemical formulae, as follows:



Prednisolone



Prednisolone acetate

These two compounds have different molecular weights (358.44 versus 402.48), different chemical properties, and different names. Additionally, page ix and Monograph 7807 of the 13th edition of the Merck Index (cited with the March 1, 2006 Reply and Amendment) makes clear that the 21-acetate derivative of prednisolone, like the other 6 compounds listed in bold under Monograph 7807, is a derivative of prednisolone rather than synonymous with such compound.

Synonyms of prednisolone and prednisolone acetate are listed in regular (i.e., unbolded) font directly following the Chemical Abstracts Registry Number (see 13th edition Merck Index at ix and Monograph 7807). Synonyms of both prednisolone and prednisolone acetate include a number of trade names for pharmaceutical products. If the term "prednisolone" were generally understood to mean "prednisolone acetate", then the buyers of these products (medical patients) would be confused, as they would be receiving the free base rather than prednisolone-17-acetate that they would understand the products to contain, or vice versa. Clearly then, these two compounds are generally considered to be distinct by physicians and by the person of ordinary skill in the art, and would be so

understood by regulatory agencies such as the U.S. Food and Drug Administration in order to protect patient health and safety. In other words, labeling a pharmaceutical product containing prednisolone-17-acetate as "prednisolone" (or vice versa) would clearly violate drug-labeling requirements as understood by those of skill in the art.

An Advisory Action mailed May 25, 2006 maintained the anticipation rejection of claim 31, arguing that "[a] generic chemical formula will anticipate a chemical species covered by the formula when the species can be "at once envisaged" from the formula", and citing a number of references said to support that position. Advisory Action of May 25, 2006 at page 2.

However, respectfully, this point is not well taken. As demonstrated by Monograph 8706 of the 13th edition of the Merck Index, prednisolone is not a "generic chemical structure", but rather a specific chemical compound having an unambiguous meaning distinct from the meaning of "prednisolone acetate" to those of ordinary skill in the art.

Therefore, Applicants respectfully request reconsideration of the outstanding rejection of claims 31-36, 39-46 and 49-50 under 35 U.S.C. §102.

For these reasons, Applicants maintain their position that Loftsson does not anticipate the present claims, incorporate by reference the arguments made in the October 6th Reply, and request the Examiner to reconsider and withdraw the rejection pursuant to 35 U.S.C. 102(b) over Loftsson.

Rejection pursuant to 35 USC §103(a)

The present claims are not obvious over the combination of Loftsson and Dzaibo because these references do not suggest the surprising finding that prednisolone acetate in formulation with cyclodextrin is able to enter the posterior segment.

The Examiner has maintained the rejection of claims 31-36, 39-46 and 49-50 as allegedly obvious over Loftsson, and claims 31, 36-38 and 46-48 as allegedly obvious over Loftsson further in light of Dziabo et al., U.S. Patent No. 5,424,078. The Examiner alleges that Loftsson et al. teaches a preserved cyclodextrin and prednisolone ophthalmic composition, and that Dziabo et al. disclose chlorite as a preservative. Applicants respectfully traverse this rejection for the following reasons.

Loftsson has been characterized above. Dzaibo discusses a stabilized chorine dioxide preservative.

As discussed above, the Loftsson reference does not disclose an ophthalmic composition containing the compound being claimed in the present claims, prednisolone acetate. This fact is supported by the 13th edition of the Merck Index, page ix and Monograph 7807, which have been made of record herein.

The Manual of Patent Examining Procedure (MPEP), relying on long-established judicial precedent, states that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so in the references or otherwise within the knowledge of the person of ordinary skill in the art. See MPEP § 2143.01. As indicated more fully below, there is nothing in Loftsson et al., or in the combination of Loftsson and Dziabo et al., that would

suggest the specifically claimed compositions containing prednisolone acetate, a compound not even mentioned in either reference, or methods of using such compositions. For this reason, the Applicants respectfully request the Examiner to withdraw this rejection and permit the present claims to proceed to issue.

Applicants have submitted with this Reply a Supplemental Information Disclosure Statement placing two references into the record. These references are Loftssona et al., Advanced Drug Delivery Review 36 (1999) 59-79 and Lyons et al., U.S. Patent Publication No. 2005/0234018.

Both of these references provide evidence that the claimed prednisolone acetate-containing compositions of the present invention yield surprising results when used as an ophthalmic composition.

Loftssona et al. discusses the use of cyclodextrins with an active drug for ophthalmic drug delivery. While the publication discusses that cyclodextrins may be useful additives in ophthalmic formulations, some disadvantages of cyclodextrin use in ophthalmic formulations are clearly disclosed in this publication. For example, *Loftssona et al.* discusses that "[i]t is generally accepted that only the free drug, and not the drug/CD complex, can penetrate lipophilic biological barriers", such as the cornea. *Loftssona et al.* at 70, second column at 8.1. Moreover, this reference discloses "corticosteroids can only be administered locally for diseases of the outer eye and anterior segments of the eye. For diseases of the posterior segments of the eye, systemic administration is required." *Id.* at 74.

However *Lyons et al.*, filed and published after the priority date of the present invention, proves otherwise. In Figure 2 of *Lyons et al.* one 35 µl drop of one of seven cyclodextrin-prednisolone acetate preparations are instilled into rabbit eyes and after 60 minutes the amount of

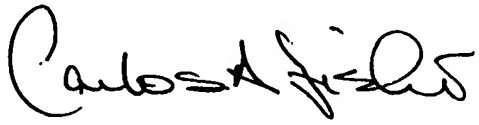
prednisolone acetate and its metabolites prednisolone and prednisone in rabbit aqueous humor is determined and the sum reported for each preparation. Figure 3 shows the results of assaying the vitreous humor of the same animals at the same time point – this time the amount of the metabolite prednisolone is determined. As can be seen, in the absence of cyclodextrin prednisolone acetate is unable to enter the vitreous (posterior) chamber (Figure 3, bar 2g). However, the compositions containing even half as much prednisolone acetate in combination with cyclodextrin show substantial infusion of the metabolite prednisolone into the posterior segment (Figure 3, bar 2b).

Thus, contrary to the prevailing opinion of the prior art, the combination of cyclodextrin with prednisolone acetate facilitates delivery of the drug to the vitreous humor and the posterior segment of the eye. These results are completely unanticipated, surprising and non-obvious in light of Loftsson and Dziabo.

CONCLUSION

For the above reasons Applicants submit that the claims hare in condition for allowance and respectfully request that the Examiner issue a notice to that effect.

Respectfully submitted,



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